REMARKS

Reconsideration of the allowability of the present application in view of the above claim amendments and the following remarks is respectfully requested.

I. Status of the Claims

Claims 23, 24, 32, and 34 were acted upon by the Examiner. Claim 23 has been amended. Claims 35-40 have been added. Accordingly, Claims 23, 24, 32, and 34-40 are presented for examination.

II. Discussion of the Amendments

The specification has been amended to remove references to hyperlink or other forms of browser executable codes. No new matter has been added.

Claim 23 has been amended to add the recitations that the administered peptide is "isolated" and that the peptide is "at least 10 amino acids" in length. Support for the amendment to claim 23 is found, for example, on page 2, lines 9-11 and page 8, lines 1-3.

New claims 35-37 are directed to methods using various purified forms of the claimed peptide. Support for new claims 35-37 is found, for example, in originally filed claims 10 and 11.

New claim 38 is directed to further fragment sizes of the claimed peptide. Support for new claim 38 is found, for example, on page 8, lines 1-6.

New claim 39 is directed to the peptide comprising SEQ ID NO:2. Support for new claim 39 is found, for example on page 17, lines 17-20.

New claim 40 is directed to a method wherein the mammal is a human. Support for new claim 40 is found, for example, on page 3, lines 14-15.

III. Discussion of Objections

The Examiner objected to the incorporation by reference of hyperlinks on page 10, lines 9 and 10. Applicants have deleted these hyperlinks and replaced them with a reference to the government provider of the databases at the hyperlinks (National Center for Biotechnology Information (NCBI) of the U.S. National Institutes of Health (NIH)). Support for this amendment is found within the hyperlinks, which contain the well known acronyms for these government sources, NCBI and NIH.

IV. Discussion of Section 112 Rejections

A. Written Description Rejection

The Examiner rejected claims 23, 24, 32 and 34 under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserted that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner asserts that the specification or claims do not provide any specific fragments that retain paralytic activity of SEQ ID NO:2, that since the claim uses open language, the claim could encompass even a single amino acid, and that the function of the fragments cannot be ascertained.

Applicants have amended claim 23 to refer to methods using compositions, "comprising at least 10 amino acids" of the amino acid sequence DCSQDCAACS ILARPAELNT ETCILECEGK LSSNDTEGGL CKEFLHPSKV DLPR (SEQ ID NO:2). Accordingly, as amended, claim 23 does not encompass an amino acid sequence of only a single amino acid. The claim also continues to recite that "the peptide has paralytic activity", which excludes non-paralytic fragments. New claim 38 recites additional ranges of fragment sizes that are at least 10 amino acids long.

The written description requirement does not require a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988). In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002), the Federal Circuit made clear that the written description requirement can be satisfied in a number of ways by disclosing, for example, "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." *See* M.P.E.P. § 2163.

Here, Applicants have provided *the complete structure* of SEQ ID. NO:2. Moreover, the application recites ranges of fragment sizes that are useful in the methods of the invention (see, e.g., page 8, lines 1-6). The application also provides examples of assays that allow a person skilled in the art to determine whether a peptide has paralytic activity (see mealworm assay on page 29, lines 1-4). This provides clear direction and guidance as to how to identify fragments of SEQ ID NO:2 that would have the claimed paralytic activity. Accordingly, applicants disclosure of the structure of SEQ ID NO:2 coupled with assays to test paralytic activity is more than enough to adequately describe the peptides to one of skill in the art within the scope of claim 23.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Enablement Rejection

The Examiner rejected claims 23, 24, 32 and 34 under 35 USC § 112, first paragraph, because the specification, while being enabling for the full length of the peptide of SEQ ID NO:2, does not reasonably provide enablement for fragments of SEQ ID NO:2.

MPEP §2164.01 provides that the test for enablement requires a determination as to whether one of skill in the art can practice the claimed invention without undue experimentation. Such is the case here.

As discussed above, Applicants have provided *the complete structure* of SEQ ID. NO:2. The application also provides examples of assays that allow a person skilled in the art to

determine whether a peptide has paralytic activity (see mealworm assay on page 29, lines 1-4). Thus, one of skill in the art would be able to identify and verify, using the assays described in the specification, a fragment of SEQ ID NO:2 that has paralytic activity.

The Examiner has not provided any reasons to support the conclusion that "there is a large quantity of experimentation necessary to determine which fragments of SEQ ID NO:2 . . . will retain paralytic activity." The M.P.E.P. makes clear that it is not the quantity of experimentation that is determinative rather it is whether such experimentation would be undue. M.P.E.P. § 2164.06 ("Time and difficulty of experiments are not determinative if they are merely routine."). Here, any such experimentation to determine which fragments would have paralytic activity would be routine to one of skill in the art. SEQ ID NO:2 contains only 54 amino acids. Accordingly, there are only forty-five 10 amino-acid fragments in SEQ ID NO:2. Synthesizing these fragments and testing them for paralytic activity using the mealworm assay described in the specification would be routine to one of skill in the art.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

V. Discussion of Art Rejections

A. Applied References

Bucherl et al.,
Venomous Animals and their Venoms, Vol. 1, Acad. Press, 1968

Bucherl et al. is a chapter from a volume regarding venomous animals and their venoms. The chapter cited by the Examiner is directed to the toxin of the short-tailed shrew, *Blarina Brevicauda*. Bucherl et al. discusses the study of two extracts from the submaxillary gland of *Blarina*: (1) an extract discussed in Pearson (1942) and (2) an extract discussed in Ellis and Krayer (1955). For the Examiner's convenience, a copy of the Pearson article has been listed on an IDS filed concurrently herewith. The Ellis and Krayer reference is already of record.

Pearson discloses a saline extract of the submaxillary gland of *Blarina*. This is a very crude extract that is prepared by grinding the gland and rinsing it with saline. Pearson merely discloses an unknown mixture of compounds, including a very large number of proteins,

peptides and other compounds. Ellis and Krayer discloses a very crude purification process of a submaxillary gland extract including dialysis and acetone precipitation. This so-called "purified" extract would contain a mixture of various proteins and other compounds. Neither Pearson nor Ellis and Krayer disclose an isolated peptide much less the isolated peptide of SEQ ID NO:2 or fragments thereof.

Kohane et al., U.S. Patent No. 6,346,020

Kohane et al. is directed to compositions causing nerve blocking wherein the nerve blocking consists of a site 1 sodium channel blocker in combination with another agent and methods of using the same. Kohane et al. does not disclose an isolated peptide of SEQ ID NO:2 or fragments thereof. Furthermore, Kohane et al. does not disclose or suggest that peptides can be used for nerve blocking or analgesia.

B. Novelty Rejection

The Examiner rejected claims 23, 24 and 32 under 35 U.S.C. § 102(b) as being anticipated by Bucherl et al. (Venomous Animals and their Venoms. Vol. 1, Academic Press, 1968). The Examiner asserts that on page 45, last paragraph, that Bucherl et al. teach that the purified toxin was concentrated, and with regards to mammals (i.e., rabbits), the lethal dose was determined. The Examiner also asserted that this toxin inherently includes the protein sequence of SEQ ID NO:2 of the instant claims because the proteins originate from the same source and has the same function.

As required by 35 U.S.C. § 102(b) and explained in M.P.E.P. § 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)." M.P.E.P. § 2131.

Claim 23 has been amended to recite methods of using an "isolated" peptide. New claims 35-37 recite additional aspects of purity of the peptides used in the methods. Here, Buschl et al. does not teach (1) an *isolated* peptide of SEQ ID NO:2 or fragments thereof or (2) methods of using SEQ ID NO: 2 for analgesia or neuromuscular blocking.

1. Buschl et al. does not teach an isolated peptide of SEQ ID NO:2

First, Buschl et al. does not even teach that the shrew toxin is a peptide or protein. Prior to this invention, there was merely speculation that the toxic shrew principle could possibly be proteinaceous. Bucherl et al. state in their introduction on page 43 that, "[t]he physical and chemical properties of toxic substances contained in the homogenates of submaxillary glands from insectivorous mammals are poorly understood. The toxin of the short-tailed shrew, *Blarina brevicauda* (Say), has been partly determined (Pearson, 1942; Ellis and Krayer, 1955), but the chemistry of even this substance is not precisely defined." Burcherl et al. states on page 44 that, the *Blarina brevicauda* toxin "may be a protein *or a substance firmly adsorbed on protein*" (emphasis added).

Second, Bucherl et al. does not expressly or inherently disclose an isolated or purified compound with paralytic activity, much less the peptide as recited in the claimed methods. Bucherl et al. is a review article that refers to Pearson (1942) which involves a saline extract of submaxillary gland of *Blarina*. This is a very crude extract that is prepared by grinding the gland and rinsing it with saline. Pearson merely discloses an unknown mixture of compounds, including a very large number of proteins, peptides and other compounds.

Bucherl et al. use the term "purified toxin" to refer to a homogenate that has had very preliminary separation steps performed on it, not a purified polypeptide. The use of one or two separation steps to produce a crude homogenate is not a "purification" or "isolation" of a peptide. In fact, the term "purified" is first introduced in the Bucherl et al. review (pg 44, para 2) in quotation marks which indicates that the homogenate itself is not considered to be accurately referred to as purified. Burcherl et al. appear to use the term "purified" because that is the term that was used by the authors of the Ellis and Krayer article discussed in Burcherl et al. (the Ellis and Krayer article is already of record). Ellis and Krayer report that, before the final dialysis and precipitation with acetone that would precipitate any proteinaceous material present in the processed gland extract, they obtained "a moderate purification" (pg 130, par. 1, line 1) and stated at line 8 that "this preparation was used in all the later experiments and is referred to as the *purified toxin*." It is clear to any person familiar with the art that the material in the "moderate

purification" would not be an isolated peptide with paralytic activity, but would be a mixture of various proteins and other compounds.

Bucherl et al. also refers to purified toxin obtained by Ellis and Krayer (1955) from an extract of submaxillary gland subjected to dialysis and then precipitated with ammonium sulfate at various concentrations. This is a crude ammonium sulfate precipitate of shrew saliva glands.

Moreover, the extracts disclosed in the Bucherl et al. review article would include other toxic compounds. For example, the Pearson extract includes *any compounds* that would dissolve, or be suspended in, saline. The Ellis and Krayer extract includes any compounds that can be obtained by dialysis and ammonium sulfate precipitation. These extracts would also include many proteins that could cause the toxicity noted in Bucherl et al. The protein components of mammalian saliva and human saliva include the enzymes amylase, rennin, kallikrein, nerve growth factor, other peptidases, peroxidase, ribonucleases, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, galactosidase, dehydrogenases, adenylate and guanylate cyclase and lysozyme, acid phosphatase. There are also a variety of small, non-proteinaceous molecules present in saliva: amino acids, glucose, glucosamine, urea, uric acid, folic acid, cholesterol, corticosteroids, oestrogens, progesterone, testosterone. Glandular extracts therefore contain many more biochemical entities than are excreted into the salivary fluid. Therefore, glandular extracts would be expected to be toxic upon injection into serum. For example, crude submaxillary gland extracts would include kalikrein-type enzyme that indiscriminately cleaves certain proteins and peptides to smaller pieces. These enzymes would cause toxicity after injection into an animal likely by cleaving functional peptides, such as signal peptides in blood.

Third, in the submaxillary gland, the amino acids sequence corresponding to SEQ ID NO:2 is not isolated, but is in an inactive form as part of large molecular weight complex (see specification at page 5, lines 25-29 and lane 1 of Figs. 2 and 3). Accordingly, a peptide useful in the claimed methods of the invention cannot be obtained merely by homogenizing and extracting the submaxillary gland (as in Bucherl et al.) since the peptide will still be in a large complex and inactive.

Fourth, Buscherl et al. teaches that the toxin is a high molecular weight protein. As described in the present application on page 1, lines 23-25, "Using a crude ammonium sulfate precipitate of shrew saliva glands, Ellis and Krayer concluded the active agent was probably a protein and, because of its inability to dialyze, a ***larger protein***." (emphasis added). In contrast, SEQ ID NO:2 is a small peptide of 6000Da.

Finally, as further evidence that the crude "purification processes" of Pearson and Ellis and Krayer do not disclose an *isolated* peptide of SEQ ID NO:2 or a fragment thereof, Applicants' isolation of the paralytic peptide was not routine. For example, isolation of the SEQ ID NO:2 peptide from an unusual combination within a large protein complex was unexpected. The present patent application states on page 6, lines 1-5, "Unexpectedly, the small active component exists as part of a very high molecular weight, multiprotein complex (Fig. 2; Fig. 3, lane 1) the molecular weight of the complex was about 600,000 daltons. It appeared in a void volume fraction from a size exclusion column (Sephadex G-200) that has a molecular weight cut-off of 600,000 daltons." Because no paralytic activity was found in the small peptide region of the size exclusion chromatographic analysis, one would not have expected the toxin to be a small peptide.

Accordingly, the extracts of Pearson and Ellis and Krayer discussed in Bucherl et al. do not expressly or inherently disclose the claimed *isolated* compounds of SEQ ID NO:2 or fragments thereof, and thus, for this reason alone, the anticipation rejection should be withdrawn.

2. The peptide of SEQ ID NO:2 is not necessarily present in shrew saliva

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. . . . To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" M.P.E.P. § 2112 (citations omitted).

Here, Pearson and Ellis and Krayer examined glands, and not saliva. Thus, they did not determine whether any of the compounds in their crude extracts actually leave the gland, enter the saliva and are injected into the bitten (or injected) subjects. In contrast, the present Applicants analyzed the toxin of the invention from the submaxillary gland and shrew saliva (e.g., Fig. 6). This proved that the Applicants isolated the shrew toxin amino acid sequence. Detection of the shrew paralytic peptide in saliva confirmed that the Applicants had isolated the shrew's paralytic toxin, rather than a glandular compound that has toxic effects.

In fact, the claimed compound is **not** stored in an active form in submaxillary saliva glands. The compound is only present as an inactive, larger protein. The compound of the invention has a structure that has similarity to a short sequence of mammalian preproenkephalin that is initially synthesized in mammalian salivary glands having a sequence of more than 200 amino acids which is subsequently processed by the cell machinery to produce short peptide enkephalins and, the compound of the invention. See, for example, the statement on page 25, lines 16-18 that, "Warming the crude extract at 40°C for 20 minutes increases the amount of isolatable peptide. Without wishing to be bound by theory, it appears that the bioactive peptide is kept complexed in the salivary gland until it is released as an active form in the saliva."

Accordingly, the peptide of SEQ ID NO:2 is not necessarily present in the extracts of Pearson and Ellis and Krayer.

3. Buschl et al. does not teach a method of analgesia or neuromuscular blocking

The Examiner further asserted on page 46, third paragraph from the bottom, that the effects of the venom of *Blarina* are discussed regarding changes in circulatory and respiratory systems of rabbits. The Examiner also notes that on page 48, second paragraph from the bottom, the effect of the venoms of shrews on experimental animals is discussed, such as paralysis of hind limbs and convulsions, where the intensity of reaction depended on the size of the dose and the site of administration, where the most effective were the intravenous injections of extract of the submaxillary glands of *Blarina*.

For the reasons explained above, Bucherl et al. does not disclose that the peptide that causes paralysis is the isolated sequence of SEQ ID NO: 2. Bucherl et al. describes toxic or lethal effects of administering crude extracts of shrew gland. There is also no disclosure or suggestion that in Bucherl et al. that administering the crude extracts described therein will produce therapeutic analgesia or neuromuscular blocking. Indeed the crude nature of the compounds and the potentially fatal symptoms that occurred in animals after injection (e.g. changes in circulatory and respiratory systems, convulsions) would clearly indicate to one of skill in the art that the compounds could not be used for therapeutic analgesia or neuromuscular blocking. This is reflected by the fact that, even though the cited art was published many years ago, the Examiner has not located any subsequent literature about the potential use of shrew toxin for analgesia.

In summary, Bucherl et al. does not expressly or inherently disclose the presently claimed isolated peptide used in the methods of the invention. A crude extract is not an isolated peptide and cannot anticipate a claim for an isolated peptide. Moreover, there is no disclosure in Bucherl et al. that administering the crude extracts described therein could be used for therapeutic analgesia or neuromuscular blocking. Accordingly, this anticipation rejection should be withdrawn.

C. Obviousness Rejection

Claims 23 and 34 were rejected under 35 USC 103(a) as being unpatentable as obvious over Bucherl et al. in view of Kohane et al. (US 6,326,020). The Examiner concedes that the teachings of Bucherl et al. do not teach a method of dosing a mammal in pain. The Examiner, however, asserts that Kohane et al. teach different nerve blockers that were used in animal models to make animals insensitive to pain. The Examiner further asserts that it would have been obvious to one skilled in the art to design a method where the paralytic peptide as taught by Bucherl et al. is administered to a mammal to alleviate pain.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Here, as discussed above, Bucherl et al. does not disclose a number of the elements of the claimed invention, particularly (1) an isolated peptide of SEQ ID NO:2 or fragment thereof or (2) a method of using SEQ ID NO:2 or fragment thereof for analagesia or neuromuscular blocking. Moreover, there would be no reason or expectation of success in combining the teachings of Bucherl et al. and Kohane et al. to derive Applicants' claimed invention. Finally, the claimed peptides provide unexpected and surprisingly strong results in methods of analgesia and neuromuscular blocking.

As discussed briefly above, Kohane et al. is directed to compositions causing nerve blocking wherein the nerve blocking consists of a site 1 sodium channel blocker in combination with another agent. The listed toxins are all small organic molecules that are structurally and chemically very different from proteinaceous toxins. The teachings of Kohane et al. are limited to formulations and methods using such small organic compounds. Kohane et al. does not suggest that proteinaceous compounds can be used to make animals insensitive to pain. As a result, Kohane et al. does not teach or suggest an isolated peptide of SEQ ID NO:2 or fragments thereof in a method of analgesia or nerve blocking. Accordingly, a combination of Kohane et al. with Bucherl et al. would not teach or suggest all the claim limitations of clam 23 and its dependent claims. For this reason alone, the obviousness rejection must be withdrawn.

There would be no reason to combine Burcherl et al. and Kohane et al. or any expectation that such a combination would be successful in resulting in Applicants' claimed method. The teachings of Kohane et al. are limited to formulations and methods using such small organic compounds. Kohane et al. does not suggest that proteinaceous compounds can be used to make animals insensitive to pain. It cannot be assumed that any toxin is useful for providing analgesia and neuromuscular blocking. The cited art provides no suggestion or motivation for analgesic or neuromuscular blocking uses of shrew toxin or suitable compositions and doses for such uses.

There would therefore be no motivation to combine Kohane et al. with Burcherl et al. and no reasonable expectation of success.

Moreover, the claimed compounds provide surprisingly strong results by producing a long lasting activity (for example, Fig. 14 discussed on page 29, lines 1-3 shows that paralytic saliva administered to a mealworm can keep it alive, with total paralysis, for at least 7 days). Some prior art suggests a short duration of action. For example, Dufton reported a short period of paralysis in data obtained from worms and fly maggots retrieved from a captive common shrew (*Sorex araneus*) immediately after they had been bitten. The first few maggots retrieved showed evidence of paralysis, but recovered after a few hours. Subsequent maggots retrieved showed no signs of immobilization. No profound effects were seen with worms. The present Applicants have thus for the first time identified the unexpected and surprisingly strong results obtained with the compounds of the invention.

Accordingly, the obviousness rejection of claims 23 and 34 should be withdrawn.

VI. Conclusion

In view of Applicant's claim amendments and the arguments presented above, the present application is believed to be in condition for allowance and an early notice thereof is earnestly solicited. Applicants request that the Examiner contact the undersigned before issuing another action.

Respectfully submitted,

/Marc S. Segal/
Marc S. Segal
Reg. No. 40,163

Synnestvedt & Lechner LLP
1101 Market Street, Suite 2600
Philadelphia, PA 19107
Telephone: (215) 923-4466
Facsimile: (215) 923-2189